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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte DIDIER TRONO and PATRICK SALMON

Appeal 2007-2719
Application 10/010,081
Technology Center 1600

Decided: April 29, 2008

Before, DONALD E. ADAMS, DEMETRA J. MILLS, and ERIC GRIMES, *Administrative Patent Judges*.

MILLS, *Administrative Patent Judge*.

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134. The Examiner has rejected the claims for obviousness and obviousness-type double patenting. We have jurisdiction under 35 U.S.C. § 6(b). We affirm the rejection for obviousness-type double patenting but reverse the rejections for obviousness.

Representative claims follow.

7. The transduced cell of claim 30, wherein the promoter is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 40 and about 200.

19. The transduced cell of claim 30, further comprising a posttranscriptional regulatory sequence positioned to promote the expression of the transgene.

30. A human hematopoietic cell transduced with a self-inactivating recombinant lentivirus, the lentivirus comprising an expression cassette comprising a transgene positioned under the control of a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in both a human hematopoietic progenitor cell and a differentiated hematopoietic cell; and an LTR region that has reduced promoter activity relative to wild-type LTR, wherein the human hematopoietic cell is a human hematopoietic progenitor cell.

32. A method for transducing a human hematopoietic stem cell comprising the steps of:

(i) contacting a population of human cells that include hematopoietic stem cells *in vitro* with a lentiviral vector under conditions to effect the transduction of a human hematopoietic progenitor cell in said population by said vector, wherein the lentiviral vector is defined as a self-inactivating recombinant vector comprising:

(a) an expression cassette comprising a transgene positioned under the control of a promoter that is that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in a differentiated hematopoietic cell active to promote detectable transcription of the transgene in a human hematopoietic progenitor cell; and

(b) an LTR region that has reduced promoter activity relative to wild-type LTR; and

differentiating the transduced stem cell into a differentiated hematopoietic cell.

Cited References

Romain Zufferey et al., *Self-Inactivating Lentivirus Vector for Safe and Efficient In Vivo Gene Delivery;* J. Virol, 72(12):9873-9880 (1998) (hereinafter Zufferey I).

Albert B. Deisseroth, *Clinical Trials Involving Multidrug Resistance Transcription Units in Retroviral Vectors*; Clinical Cancer Research 5:16007-1609 (1999).

L-J Chang et al., *Efficacy and safety analyses of a recombinant human immunodeficiency virus type 1 derived vector system;* Gene Therapy 6:715-728 (1999).

Romain Zufferey et al., *Woodchuck Hepatitis Virus Postranscriptional Regulatory Element Enhances Expression of Transgenes Delivered by Retroviral Vectors*; J. Virol 73(4): 2886-2892 (1999) (hereinafter Zufferey II).

Case et al., *Stable transduction of quiescent $CD34^{+}CD38^{-}$ human hematopoietic cells by HIV-1-based lentiviral vectors;* Proc. Nat'l Acad. Sci. USA 96: 2988-2993, (1999).

Grounds of Rejection

1. Claims 4-5, 7-10, 12, 19, 22-23, 25, 30-34 and 38-45 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 113-123 of Application Serial No. 10/261,078.

2. Claims 4-5, 7-8, 12, 25, 30-34 and 38-45 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth.

3. Claims 7-10 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth and Chang.

4. Claims 19, 22 and 23 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth and Zufferey II.

DISCUSSION

Background

"The present invention relates to improved lentiviral vectors and their use in gene delivery and high level expression of desired transgenes to target cells, particularly to human hematopoietic progenitor cells and differentiated blood lineages." (Specification 1.)

"Gene therapy via the transduction of human hematopoietic stem cells (hHSC) represents a very promising approach for the treatment of a number of inherited and acquired lympho-hematological disorders. The stable genetic manipulation of long term repopulating hHSC with existing gene delivery systems, however, has been impossible to achieve at an efficiency compatible with therapeutic realities." (*Id.*)

1. Claims 4-5, 7-10, 12, 19, 22-23, 25, 30-34 and 38-45 stand rejected under the judicially created doctrine of obviousness-type double patenting over claims 113-123 of Application Serial No. 10/261,078. Application Serial No. 10/261,078 issued as United States Patent No. 7,198,950 on April 3, 2007.

Claim 1 of the '950 patent reads as follows.

1. An in vitro hematopoietic progenitor host cell transduced with a lentivirus comprising a transgene positioned under the control of a promoter that is active to support expression of the transgene in blood cell derivatives of said progenitor, and capable of promoting expression of the transgene in the hematopoietic progenitor cell at a signal-to-noise ratio of between about 10 and about 200.

The Examiner argues that "[a]lthough the conflicting claims are not identical, they are not patentably distinct from each other because the scope of transduced host cells and the method of transducing human hematopoietic stem cells as claimed in the [patent] encompasses the host cells and method of transducing human hematopoietic stem cells as claimed in the instant application." (Ans. 4.) We find no error in the Examiner's obviousness-type double patenting rejection.

In response to the obviousness-type double patenting rejection Appellants argue that a terminal disclaimer will be submitted when Application Serial No. 10/261,078 is allowed. (Br. 6.)

Since Appellants do not address the merits of the obviousness-type double patenting rejection in the Brief, the rejection is affirmed.

2. Claims 4-5, 7-8, 12, 25, 30-34 and 38-45 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth.

The Examiner finds that

> Zufferey [I] teaches self-inactivating HIV-1 based lentivirus vector (SIN) comprising the HIV-1 back bone containing HIV-1 gag, pol and rev genes … The cited art further teaches that the SIN vectors contains a 400-nucleotide deletion in the 3' LTR which renders the LTR inactive as compared to wild type LTR … The cited art further teaches that the SIN lentiviral vector comprises the CMV internal promoter, wherein the CMV promoter is inherently known to promote detectable transcription of a transgene in human hematopoietic progenitor cells upon transduction with a lentiviral vector … In addition the cited art teaches transduction of human PBLs and human lymphocytic SupT1 cells using the SIN expression vector (page 9875, table-1; page 9878 fig-4). The cited art further teaches that inactivation of LTR provides higher signal to noise ratio

> which falls in the range of about 10 to about 200 (see page 9876 table 2).

(Ans. 5.)

The Examiner acknowledges that Zufferey I does not teach the transduction of hematopoietic stem cells comprising a self inactivating SIN-lentiviral vector or a transgene which is a multidrug resistance gene (MDR). (Ans. 5.)

Thus, the Examiner relies on Deisseroth for its teaching of

> clinical trails involving multidrug resistance transcription units encoded in retroviral vectors. The cited art teaches the use of retroviral vectors to transfer human MDR-1 into human hematopoietic stem cells in-vitro (page 1607, col. 1 para 4; col. 2 para. 2). The cited art further teaches clinical trials, which show engraftment of vector modified clonogenic hematopoietic progenitor cells into human patients (page 1608, col.1). The cited art further teaches the use of lentiviral vectors to transduce early hematopoietic stem cells, which resulted in the transduction of at least 80% of CD34+/CD38- hematopoietic stem cells (page 1608, co1. 2 para. d).

(Ans. 5.)

The Examiner concludes that

> it would have been obvious to one ordinary skill in the art at the time of filing to modify the invention of Zufferey [I] by substituting the GFP reporter gene with a MDR gene and hematopoietic cells with hematopoietic stem cells in view of Deisseroth. It would have been further obvious to differentiate the transduced stem cell into different lineages, since hematopoietic stem cells have clonogenic potential. One would have been motivated to do so, since the transduction of human hematopoietic progenitor cells with the MDR-gene decrease the toxicity of chemotherapeutic agents in hematopoietic cells and

> differentiated cells. One would have a reasonable expectation of success in doing so, since retrovirus induced transduction of human progenitor cells (to express a gene of interest) has been routine in the art at the time of instant invention.

(Ans. 5-6.)

When determining whether a claim is obvious, an Examiner must make "a searching comparison of the claimed invention – *including all its limitations* – with the teaching of the prior art." *In re Ochiai*, 71 F.3d 1565, 1572 (Fed. Cir. 1995) (emphasis added). Thus, "obviousness requires a suggestion of all limitations in a claim." *CFMT, Inc. v. Yieldup Int'l Corp.*, 349 F.3d 1333, 1342 (Fed. Cir. 2003) (citing *In re Royka*, 490 F.2d 981, 985 (CCPA 1974)).

Regarding claims 30 and 32, we do not find the Examiner has established a prima facie case of obviousness on the evidence before us. In particular we do not find the Examiner has adequately addressed the claim limitation requiring a promoter that is capable of promoting expression of the transgene at a signal-to-noise ratio of between about 10 and about 200 in both a human hematopoietic progenitor cell and a differentiated hematopoietic cell. The Examiner argues in the Answer that "the signal-to-noise ratio" is merely an "arbitrary value that not only depends upon the choice of transgene and/or host cell, but is also upon the sensitivity of the instrument and methodology used." (Ans. 10.)

The Specification, however, defines the signal-to-noise ratio as the "mean of fluorescence intensity of GFP^+ cells divided by mean of fluorescence intensity of GFP^- cells." (Spec. 57.) Therefore the

Specification provides a specific meaning for the term "signal-to-noise ratio." Claim construction begins with the words of the claim. *Rexnord Corp. v. Laitram Corp.*, 274 F.3d 1336, 1341 (Fed. Cir. 2001). Generally, terms in a patent claim are given their plain, ordinary, and accustomed meaning to one of ordinary skill in the relevant art. *Id.* After identifying the plain meaning of a disputed claim term, the court examines the written description and the drawings to determine whether use of that term is consistent with the ordinary meaning of the term. *Day Int'l, Inc. v. Reeves Bros., Inc.*, 260 F.3d 1343, 1348 (Fed. Cir. 2001). This heavy presumption in favor of the ordinary meaning of claim language as understood by one of ordinary skill in the art is overcome: (1) where the patentee has chosen to be his or her own lexicographer by clearly setting forth an explicit definition for a claim term. *Johnson Worldwide Assocs., Inc. v. Zebco Corp.*, 175 F.3d 985, 990 (Fed. Cir. 1999).

Appellants argue the Specification demonstrates that the CMV promoter is unfit for use in haematopoetic progenitor cells. (Br. 9.) Appellants further argue that through the inclusion of the signal-to-noise ratio limitation, the claims have been drafted to exclude the use of the CMV promoter. (Br. 9.) We find the Examiner has not explained how the cited combination of references meets the claimed signal-to-noise ratio of claims 30 and 32. Nor do we find the Examiner has provided evidence in the prior art of a method of transducing a hematopoietic stem cell including a step of differentiating the transduced stem cell into a differentiated hematopoietic cell, as set forth in claim 32.

In view of the above, the obviousness rejection is reversed.

3. Claims 7-10 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth and Chang.

The Examiner finds that Zufferey I and Deisseroth teach a hematopoietic stem cell transduced with self-inactivating HIV-1 based lentivirus vector, but do not teach a lentiviral vector, wherein the EF-1α promoter directs the expression of a transgene. (Ans. 6.) According to the Examiner

> Chang teaches a HIV-1 derived vector system comprising pTVΔEFGPF genetic construct, which comprises human elongation factor 1α promoter (page 126, col. 1 para. 1, line 21-26). The cited art further teaches the transduction of human CD34+ hematopoietic stem cells using pTVΔEFGPF lentiviral vector, wherein the transduced progenitor cells express the GFP transgene under the control of the human eleongation [sic] factor lα promoter (page 718. col. 2 para. 2; pager 723, fig-5). … [T]he cited art teaches that human hematopoietic progenitor cells express the GFP transgene expression under the control of an EF-lα promoter, wherein the signal to noise ratio of the expressed GFP falls with the range of about 10 and about 200 (page 723, fig-5 see inset a-d).

(Ans. 6.)

Appellants argue that the lentivector employed by Chang was not a SIN design, which can have a substantial effect on promoter behavior and transgene expression, and thus there is no way to predict in advance of the present application that the promoters taught by Chang could be used advantageously in the context of the SIN design. (Br. 13.) Appellants further argue that the effect of U3 deletion (as in SIN vectors) on promoter

activity is variable depending on the promoter and cell type in question (Reply Br. 7), citing Zufferey I, page 9877, Table 3 as evidence of varying promoter activity depending upon cell type. Because Chang does not use the SIN vector construction, Appellants argue that there is no way to predict the behavior (signal-to-noise ratio) provided by the EF-lα promoter in hematopoietic progenitor cells in the context of the SIN design. (Br. 13.)

Based upon Appellants' evidence of unpredictability of promoter activity within the SIN vector design, we agree with Appellants and find the Examiner has not carried the initial burden of explaining how the cited combination of references meets the claimed signal-to-noise ratio limitation. We do not find that Chang makes up for the deficiency of the primary combination of references. For the reasons with respect to claim 30 discussed above, the obviousness rejection is reversed.

4. Claims 19, 22 and 23 stand rejected under 35 U.S.C. § 103(a) as obvious over Zufferey I in view of Deisseroth and Zufferey II.

The Examiner cites Zuffery II only for its disclosure of a posttranscriptional regulatory element that promotes the expresssion of a transgene. (Ans. 8.) Again, we find the Examiner has not explained how the cited combination of references meets the claimed signal-to-noise ratio limitation. We do not find that Zufferery II makes up for the deficiency of the primary combination of references. For the reasons with respect to claim 30 discussed above, the obviousness rejection is reversed.

SUMMARY

The obviousness obviousness-type double patenting rejection is affirmed. The obviousness rejections are reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a)

AFFIRMED

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